PREVENTION OF ENVIRONMENTAL TOBACCO SMOKE (ETS) EXPOSURE IN CHILDREN AGE 0 – 12 MONTHS;
THE DC-STEP: "HEALTHY INFANTS AND MOTHERS PROGRAM". IRB #040406

A. SPECIFIC AIMS

ETS exposure is a major public health concern, and tobacco use is one of the 10 Healthy People 2010 leading health indicators[1]. Despite the body of evidence showing the adverse effects of in-utero and postnatal exposure to tobacco smoke products (TSP) and environmental tobacco smoke (ETS) to the respiratory health in children, studies continue to be needed to elucidate when TSP exposure causes the greatest damage, possible mechanisms that underlie the damage, and how harm to the respiratory system of infants and vulnerable children can be prevented [2]. And, while some efforts to reduce prenatal and childhood ETS exposure over the past decade have been successful, there is a paucity of randomized, controlled, intervention studies in the literature targeting ETS exposure reduction among infants age 0-12 months [3-6]. Moreover, the effectiveness of ETS exposure prevention interventions in reducing the occurrence or severity of health symptoms and outcomes has rarely been systematically evaluated [5].

Primary & Secondary Aims: The primary specific aim of this study is to test the efficacy of a brief, clinic-based intervention to prevent ETS exposure during infancy that is consistent with clinical practice guidelines [7]. The secondary, exploratory aim is to assess the number and types of health effects, major and minor, associated with prenatal and postpartum exposure to TSP and ETS among infants.

> **Specific Aim #1**- Test the efficacy of a brief, clinic-based intervention to prevent ETS exposure during infancy that is consistent with clinical practice guidelines.
>
> **Exploratory Aim #2**- Assess the frequency and types of health effects, major and minor, associated with prenatal and postpartum exposure to tobacco smoke products (TSP) and environmental tobacco smoke (ETS) among infants.

We will additionally explore dose-response relationships and mediating factors among the intervention group women, and infant safety/development effects among control group women.

B. BACKGROUND & SIGNIFICANCE

B.1. Prevention of Infant Exposure to Environmental Tobacco Smoke (ETS)

Infant exposure to ETS during the first year of life is most likely to occur through: (1) maternal smoking, (2) other household members smoking inside the home including a partner/spouse or family and friends who visit the home regularly, or (3) through ETS exposures outside the home (e.g., daycare, grandmother, etc.).

B.1.1. Health Risks and Consequences of Infant ETS Exposure. Prenatal smoke exposure of the fetus and ETS exposure of children causes significant harms in both the short- and long-term [8-18]. There is strong evidence that these exposures are associated with increased rates of respiratory illness, ear infections, tonsillectomy and adenoidectomy, asthma, and sudden infant death syndrome (SIDS), and health care utilization and hospitalizations [12, 19-23]. ETS exposure causes asthma symptoms in an estimated 200,000 to 1,000,000 children, and as many as 8,000-26,000 new cases of asthma each year [24], resulting in considerable expenditure of healthcare dollars. In 1993 alone, ETS exposure of children resulted in annual direct medical expenditures of $4.6 billion and loss of life costs of $8.2 billion [25].

Health risks associated with ETS exposure during the prenatal and postpartum period are difficult to differentiate given that many women who smoke prior to pregnancy quit at varying time points during their pregnancy, and among those who quit smoking during pregnancy, large numbers relapse throughout the first year postpartum. This is true particularly among African American women [26, 27]. Depending on the population, approximately 20-30% of women relapse within the first 6 weeks postpartum, 40-50% by 6 months postpartum, and over 70% by 12-18 months postpartum [28, 29].

These progressively increasing relapse rates were further documented in a study of infants in which the amount of ETS absorption, as indicated by infant urinary cotinine excretion [30] was measured. In this study, urinary cotinine increased from 53% to 77% (95% CI of difference: 14, 35) during the first year of life; most infants (92%) excreting cotinine at 3 weeks of age were doing so at age 1 year. In addition to this continued exposure of children in their first year of life, 61% of infants not excreting cotinine at age 3 weeks were excreting it at age 1 year; reflecting maternal relapse and/or exposure to other sources of tobacco smoke; the percent of infants exposed to any ETS increased from 39% to 63% 3 weeks to 1 year [30]. Finally, the relative risks of pre- versus postnatal tobacco exposure on children have not been fully differentiated. This study will provide important data toward this goal and others.

B.1.2. Abbreviated Summary of Interventions To Reduce Infant & Child ETS Exposure. Few intervention studies specifically focused on preventing ETS exposure during infancy exist [3-6]. Most ETS intervention studies were conducted with older children, and investigated minimal contact, physician-delivered, office-based interventions**,** although some have been conducted in homes or have been more intensive [31]. The ETS prevention studies to date can generally be classified into one of four types; 1) behavioral counseling approaches, 2) brief, minimal contact interventions, 3) feedback and monitoring interventions, and 4) multicomponent interventions **(see Appendix A; Attachment A: Summary of ETS Prevention Intervention Effectiveness).** Relatively few trials of clinicians' one time counseling interventions have demonstrated positive findings and few controlled studies of repeated session counseling interventions have been completed to determine efficacy for ETS exposure reduction, though evidence is promising [32, 33]. More effective interventions tend to use more rigorous study designs, are of greater intensity and duration and they tend to be based on sound behavior change theory.[3-5, 34-49]**.**

Four randomized intervention studies identified in the literature provided promising results or used strategies warranting further investigation.[3, 4, 37, 122] In one of the most effective studies reported to date, 7 counseling sessions over a 3 month period with n = 108 ethnically diverse low income women reporting ETS exposure who had children under age 4 yielded reductions in children's mean urine cotinine concentrations in the intervention group, and increases in the control group. Changes in mean urine cotinine concentrations in the counseled group from 10.93 ng/ml at baseline to 10.47 ng/ml at 12 months, compared to increased urine cotinine concentrations in the controls from 9.43 ng/ml to 17.47 ng/ml (differences between groups by time $p<0.01$) were observed.[37]. At 12 months the cotinine concentration in the counseled group was 55.6% (48.2% to 63.0%) that of controls. A second study was a low intensity office-based intervention targeting mothers during well-baby visits who smoked >10 cigarettes per day. This intervention provided physician feedback on child urine cotinine levels to mothers, and mailed letters to families with ETS exposure reduction messages. Results suggested a 6% lower mean log ratio of the follow-up to initial urine cotinine measurements among 52 mother-child pairs randomized to the intervention group compared to control group (51 pairs) women, although these findings were not statistically significant [4]

In a third study, parents/caregivers of children age 1-3 (n= 291) were randomized to receive feedback on household air nicotine levels, combined with a 30-45 minute Motivational Interviewing (MI) sessions, and 4, 10 minute follow-up telephone counseling calls versus a self-help comparison group resulted in significant reductions in 6-month household air nicotine exposure levels for the MI group in both the kitchen (2.6 $\mu g/m^3$ vs. 6.9 $\mu g/m^3$; $F(1236) = 5.5$; $P <.05$) and TV room (2.3 $\mu g/m^3$ vs. 3.5 $\mu g/m^3$; $F(1235) = 5.04$; $P <.05$) [122]. Finally, one multi-component randomized intervention study (n=251 tx; n=242 Ctl) to prevent asthma in high risk infants combined home visits and household assessments with feedback and counseling on ways to remove house dust mite and pet allergens. The ETS intervention resulted in a significant (P= .04) reduction in the risk of asthma and rhinitis without apparent colds at the age of 12 months [3].

Interventions To Prevent Postpartum Relapse. Similarly, few postpartum relapse prevention interventions have been reported in the literature. Interventions provided only during the prenatal period to prevent relapse have generally been ineffective [50-53]. Counseling interventions conducted primarily postpartum demonstrated short-term intervention effects that were generally not maintained at a 12 month follow-up [42, 54-56]. Interventions incorporating both prenatal and postpartum intervention components were able to delay, but not necessarily prevent, postpartum relapse to smoking, although a provider delivered point-of-service intervention during pre-partum, inpatient postpartum, and well-baby visits yielded modest differences in sustained abstinence between 6 and 12 months postpartum, but not in point prevalence abstinence at 12 months [57]. A more detailed review is presented in Appendix A **(see Appendix A, Attachment B: Summary of Postpartum Relapse & Postpartum Relapse Prevention Intervention Effectiveness)**

Implications for Infant ETS Prevention Interventions. In order to prevent children's ETS exposure, evidence to date suggests that ETS intervention studies should incorporate the following in order to maximize success: (1) length and intensity of intervention sessions; (2) multimodal approaches (e.g., telephone, clinic counseling, home visits),[42, 58] (3) delivery during prenatal and immediate postpartum visits, as well as well-baby visits [57] (4) theory-based, (5) use of environmental control/stimulus cue strategies (household rules, signage), (6) ecological in orientation (addressing the family unit vs individual), (7) provide feedback on ETS exposure, and (8) address those factors found to be most highly correlated with postpartum relapse (e.g., pre-pregnancy smoking and addiction levels, smoking by partners and significant others, stress and social support, confidence and motivation to remain smoke free, and sustained breastfeeding) [26, 27, 40, 42, 52, 56, 58-63]. Implementation costs and generalizabilty to primary care settings are also important [57].

C. PRELIMINARY STUDIES & COLLABORATORS.

This study builds upon two prior studies, also funded by NICHD, to reduce infant morbidity/mortality among minority populations in the District of Columbia. In Phase I, collaborating institutions completed the *Pride in Parenting* study and in Phase II the *DCHOPE* study was completed. In this phase, Phase III, the GWU investigators will conduct two studies; one focused on providing Nicotine Replacement Therapy to heavy smokers during pregnancy, and this study, which focuses on the prevention of ETS exposure during infancy. The results from the Phase I and II studies, particularly DCHOPE, will be referred to at various points in this protocol, since the data and findings from those studies informed this ETS study.

Collaborating Institutions. This study is a cooperative agreement. Investigators at other institutions in the District of Columbia will collaborate on this study. Other collaborating institutions and research investigators include Georgetown University which will collaborate in development and safety intervention oversight and will hire the home visitors to conduct home visit assessments (they have deferred to GWU as the IRB of record), Children's Hospital which will collaborate in the development of measures, the completion of telephone interviews, and the health outcomes study analysis (under an umbrella agreement, they have deferred to GWU as the IRB of record), Research Triangle International (RTI) which is the data coordinating center and provides assistance with development of measures, data monitoring and study implementation protocols and procedures (RTI has their own IRB that will review all protocol modifications independently, after the GWU IRB committee has approved modifications), and the NICHD which is the funding institution and collaborates by providing scientific oversight to the study (the NICHD has their own scientific review committee, referred to in these documents as the Special Emphasis Panel, and they have their own IRB committee that will review all protocol modifications independently after the GWU IRB committee and the RTI IRB committee have approved modifications). All intervention staff, research team members, and home visitors will receive training and oversight from the PI, Co-PI, Co-Investigators and the collaborating institutions.

Principal and Co-Principal Investigators. Dr. Blake, the PI of this study, is a co-investigator on the previous *DCHOPE* intervention trial, and in consultation with Drs. Joseph, El-Mohandes, Windsor, and Boyd, was responsible for developing the active and passive smoke intervention and the TSP and ETS outcome measures. Dr. Blake is now collaborating with Dr. Dana Best from Children's Hospital, the Co-PI of this study, Dr. Joseph and others on DCHOPE baseline manuscripts describing correlates of spontaneous quitters and ETS exposure avoidance among non-smokers at risk, and has published in HIV/pregnancy prevention, adolescent and cardiovascular health [64-76]. Dr. Best is the PI of a national effort to train pediatric clinical providers in methods of reducing ETS-exposure of children (in collaboration with the American Academy of Pediatrics and the American Academy of Allergy, Asthma, and Immunology; funded by the US Environmental Protection Agency), and has been active in the topic of ETS exposure of children [77]. She will oversee work related to Specific Aim # 2; the health outcomes component.

GWU Co-Investigators. Dr. El-Mohandes who worked on the Phase I, *Pride in Parenting* study and the *DCHOPE* Intervention trial, will bring considerable experience in clinical neonatology to the ETS and control intervention and associated measures in this study [96-98]. Dr. Windsor will also serve as Co-Investigators on this study. They have conducted multiple smoking cessation intervention trials with pregnant women, [78-93] and concluded in a recent meta-analysis that studies of relapse prevention during pregnancy and the postpartum period should be a priority since few intervention studies have been conducted to date, [88] particularly interventions to prevent relapse among women who quit smoking spontaneously after learning they were pregnant (15% to 42% of pregnant women) [50, 94, 95].

Other Investigators/Consultants. Michele Kiely, the NICHD PI, will oversee scientific activities on behalf of the funding agency. Dr. Katz, Ph.D., a Clinical Psychologist from Georgetown University, who worked on the Phase I, *Pride in Parenting* study and served as the DCHOPE Intervention trial Intervention Supervisor, will bring considerable experience in early child development to the ETS control group intervention and associated measures in this study [96-98]. Children's Hospital Medical Center, one of the funded sites, will have responsibility over the telephone data collection staff, as was the case for the DC-HOPE Intervention trial. Nabil El- El-Khorazaty, Ph.D. and Jutta Thornberry from Research Triangle Institute will oversee data coordinating center activities.

Dr. Hovell, from San Diego State University, who has conducted numerous ETS measurement [104-108] and intervention studies [31-33, 37, 38, 47, 109-111] to prevent ETS exposure during childhood, will serve as a consultant investigator to this study. He will provide advice to improve the reliability and validity of our ETS self-report and biomarker outcome measures (DCHOPE study measures were insufficiently sensitive to low levels of TPS/ETS exposure), assist in planning for data analysis, and advise investigators on ways to incorporate ETS strategies found successful in previous interventions. Additional consulting investigators with expertise in environmental and biomarker analysis (e.g., cotinine, nicotine monitors) will participate in data analysis planning and publications focused on their respective areas of expertise.

D. RESEARCH DESIGN & METHODS

D.1 ETS Study Overview & Timeline.

Two interrelated studies will be conducted in this study: 1) a randomized behavioral intervention trial to reduce ETS exposure of children age 0-12 months using a repeated measures design, and 2) a prospective cohort study to assess the number and types of health effects, major and minor, associated with prenatal and postpartum exposure to TSP and ETS among infants in the first year of life.

The study will require five years. During the first phase, study measures and intervention procedures will be refined. We will pilot-test the entire program with 30 women; to include study recruitment, measures, intervention procedures, and data management systems, and staff training protocols before enrolling women into the main ETS study. During the second phase, when main study participant recruitment commences, study recruitment, cohort enrollment and random assignment to intervention and control groups will continue for 2 years. If necessary, a no-cost extension will be requested from the funding agency in order to complete the 12 month follow-up measures after enrollment is completed. Cohort retention procedures, quality assurance, data processing, and analyses will be conducted continuously. Manuscript production will begin in Years 4-5 for baseline and exploratory studies. Final outcome analyses and reports will be prepared in Year 5 and 6 if an extension of the study is implemented.

D.2 ETS Study Research Design.

Specific Aim # 1: **Test the efficacy of a brief, clinic-based intervention to prevent ETS exposure during infancy that is consistent with clinical practice guidelines.** A two-group, repeated measures random assignment design will address the primary aim of the ETS study to test the efficacy of an intervention designed to prevent ETS exposure during the first year of life. Women will be classified into 3 groups based on self-reported cigarette smoking and ETS exposure and saliva cotinine validated levels, and then randomized by strata to the experimental (E) and control (C) groups. Random assignment to the ETS intervention or control groups will be stratified by cohort. The first qualified participant within each stratum of women in Cohorts 1-3 will be randomized to the intervention or control groups to assure an equal number of mother-child dyads in each strata.

Pregnant Black, African American and Hispanic women who are living in the Washington, D.C. metro area who are at least 18 years of age will be recruited through prenatal care clinics between 24-35 weeks of gestation. Based upon self-reported and salivary cotinine-verified levels of maternal smoking and ETS exposure during pregnancy, recruited mothers will be classified into one of the following three cohorts: (1) women who continue to smoke during pregnancy (who report that they smoked in the past 7 days), **or** whose salivary cotinine at the time of recruitment is ≥18ng/ml (Cohort 1: n=125); (2) women who report quitting or having reduced smoking during pregnancy, **and** whose salivary cotinine at the time of recruitment is ≤17ng/ml (Cohort 2:n=125); and (3) women who did not smoke before or during their pregnancy, but who report household ETS exposure during pregnancy, or whose partners or household members smoke, **and** whose salivary cotinine at the time of recruitment is ≤17ng/ml (Cohort 3: n=125). Women will continue to be enrolled into the study until the specified sample sizes for each of these three groups is met. The three cohorts are shown in Table 1.

While we fully recognize that overlapping maternal salivary cotinine distributions will likely exist (i.e., light smokers may have cotinine values of <10ng/ml, and women exposed to heavy household ETS may have cotinine values >10 ng/ml), the combination of self-report and cotinine data will define the cohorts. If women say they smoke, they will be considered as smokers irrespective of cotinine levels, however if they say they do not smoke, and their cotinine values exceed the cut-off point for smoking, they will be considered smokers. These three strata were selected specifically to control for prenatal TPS/ETS exposure levels, address anticipated ETS exposure levels, and to address the postpartum smoking relapse curve. We anticipate, based on the literature, that 90% of women in Cohort 1 will continue to smoke postpartum, 20-30% of pregnant women in Cohort 2 will relapse to smoking again within the first 6 weeks following delivery, 40-50% within 6 months, and over 70% by the end of the first postpartum year. [27, 29, 40] We assume that over 80% of women in Cohort 3 will have continued ETS exposure postpartum, and that 4% of women in Cohort 3 will initiate smoking at 1.5 years postpartum.[29]. Thus, infants of women in Cohorts 1-3 are at considerable risk for ETS exposure/health effects in the first year.

Table 1. Revised ETS Study Cohort Assignment.

Self-Reported TSP/ETS Status for ETS Study	**Salivary Cotinine Levels**	**ETS Study Cohort #**
Before Pregnancy Smokers, Continue to Smoke	≥30ng/ml	Cohort 1
Before Pregnancy Smokers, Continue to Smoke	≥18 and < 30ng/ml	Cohort 1 *
Before Pregnancy Smokers, Spontaneous Quitters/Reducers	≤17 ng/ml	Cohort 2
Non-Smokers Before Pregnancy, ETS Exposed	≥11 ng/ml and ≤ 17 ng/ml **	Cohort 3
Non-Smokers Before Pregnancy, ETS Exposed	≤ 10 ng/ml **	Cohort 3
Non-Smokers Before Pregnancy, Non-ETS Exposed		Ineligible ***
Not Able to Classify	NS	Ineligible

***** *In the original protocol, this group was classified as being in Cohort 2, but subsequent analyses with this population suggested that the cut-point for African American smokers was > 17 ng/ml.*

** *ROC curves of DCHOPE data showed ≥ 11 as cut-point for passive exposure, but this was with a lower value of 10 from the cotinine lab that we used as a vendor.*

*** *Previously was described as Cohort 4, but will no longer be recruited into the ETS study.*

Exploratory Aim # 2: **Assess the frequency and types of health effects, major and minor, associated with prenatal and postpartum exposure to tobacco smoke products (TSP) and environmental tobacco smoke (ETS) among infants.** It is anticipated that the above stratified sampling design will control for varying levels of prenatal cigarette smoking and ETS exposure, and depending on levels of postpartum smoking and exposure, enable an exploratory analyses of the differential impact varying levels of prenatal and postpartum exposure may have on infant health outcomes in the first year of life.

D.3. Overview of ETS Study Pilot Test. In the pilot study, we will collect qualitative information from women regarding the ETS study interventions and delivery mechanisms, focus on refinement and adaptation of measures and intervention sessions, and finalize study recruitment, retention, implementation and monitoring procedures, and staff training protocols. ETS study recruitment procedures, the intervention, and measures will be pilot tested with 10 women from each of the 3 cohorts (30 total). Discussions conducted with clinic staff and participants will assess the viability of implementing postpartum intervention sessions at prenatal care clinic sites, and solicit any concerns about our possibly providing postpartum intervention sessions at one central site. Women enrolled in the pilot study will participate between the first prenatal and second postpartum visits in all study procedures. All measures including telephone interviews, maternal saliva and infant urine cotinine assessments, household ambient nicotine monitors, and health outcome data will be collected as will be done for the main ETS study. These 30 women will continue through the course of the intervention and follow-up procedures through 12 months as main ETS study women are enrolled. Adaptations to the Phase II *DCHOPE* active/passive smoke intervention and Phase I *Pride in Parenting* intervention will be pilot-tested at the same time. Intervention pilot-testing will occur with the first n=30 women enrolled in Cohorts 1-3 of the ETS study. An additional 12 women will be recruited to conduct cognitive testing of specific survey items, instructions or informed consent text. **A further description of the pilot test protocol is attached as Appendix B.**

D. 4. ETS Study Recruitment & Retention

Selection Criteria (Inclusion/Exclusion). English-speaking women over age 18, who self-identify as African American, Black or Hispanic, live in the DC metropolitan area, and who have a singleton pregnancy will be enrolled in this study. Exclusionary criteria include women reporting diagnoses of major psychiatric illnesses, current incarceration or suicidal ideation, or who initiate prenatal care after 28 weeks. At postpartum, women who have lost custody of their child, are in withdrawal from addictive substances requiring hospitalization or methadone treatment will be deemed ineligible to remain in the study. Further, all women who report delivery complications requiring a hospital stay of 7 days or longer, or the infants' admission to the NICU (or NICU step down unit) for more than 12 hours, including infant prematurity less than 34 weeks, or infant birth weight less than 1800gm (i.e., 4.9 pounds), will be considered ineligible to continue in the study.

Four sources of information will be required to ensure eligibility. The ACASI screener will identify current, recent and passive smokers for cohort assignment. The ACASI will also screen out women who are under age 18, who do not speak English or do not identify themselves as African American, Black or Hispanic, and who report suicidal thoughts or ideation. Baseline interviews and medical record abstractions will screen out women who initiate prenatal care after 28 weeks, have a major psychiatric diagnosis, are incarcerated or are in treatment for substance abuse disorder. Postpartum interviews and medical chart abstractions for mothers and infants obtained immediately following delivery will be used to rule out mother-infant dyads who are no longer eligible to participate in the study due to delivery complications, infant admission to the NICU, premature birth, or very low birth weight.

Recruitment/Enrollment/Retention. Expectant mothers will be recruited between 24-35 weeks of gestation at the GWUMC, Providence and Chartered Health Hospitals prenatal care clinics. It is possible that a fourth site will be added (e.g., Howard University clinic or Washington Hospital Center) as we are now in discussions with those sites. All enrollment and intervention activities will be conducted by GWU ETS study research staff using GWU approved consents and measures. No one other than GWU employees and ETS study research staff from collaborating institutions will be involved in recruiting, intervening, or research assessments during the study. Clinical staff at these three facilities will not engage in research, recruitment or intervention activities.

Following a study explanation, women will complete the ACASI consent documents (**see Appendix C; Recruitment & Informed Consent Documents**). Once consent forms to answer the ACASI screening questions are signed, women will complete the ACASI screener to determine whether they are eligible to participate in the study. Included on the ACASI screener are questions related to eligibility (e.g., weeks pregnant, race/ethnic identity, multiparity), cigarette smoking and environmental tobacco smoke exposure. Also included on the ACASI screener is the Beck Depression Inventory (BDI)–FastScreen, a 7-item self-report instrument to assess the severity of depressive symptoms corresponding to the psychological, non-somatic criteria for diagnosing major Depressive Disorders in the Diagnostic and Statistical Manual of Mental Health Disorders—Fourth Edition (DSM– IV). If a woman's answers on the ACASI-screener indicate clinical depression, or if she indicates on the ACASI-screener that she is suicidal she will be immediately referred to a medical staff person at the clinic for further care or referral to care by her primary provider. Only 2 of 2,913 (0.1%) were eliminated from DCHOPE for suicidal ideation on the ACASI screener.

Women who are eligible following ACASI screener completion will then be administered a consent form to participate in the main ETS study activities **(see Appendix C; Recruitment & Informed Consent Documents**). It will be explained that the ETS study is designed to help mothers better understand and improve the health of their newborn child during the first year of life. All women will be advised that study participation is voluntary, any information obtained will remain confidential, and access to health care services will not be affected by their decision to participate. Eligible women will be fully informed about the requirements for study participation and the monetary incentives available for completion of study measures and intervention sessions.

Incentives will be provided for participation in the intervention sessions as well as the assessments. There are four intervention clinic visits planned with the Infant Health Advisor (IHA). Each time a woman attends a visit with the IHA, she will receive $20 to help her with child care and transportation. Thus, the maximum amount of incentives received for women attending all intervention visits will be $80. There are a total of 4 assessments; a prenatal baseline assessment, and at 3-months, 6-months and 12-months postpartum. All four assessments each consist of a telephone interview and two home visits one week apart. Participants will receive a total of $30 for completion of the first two assessments as compensation. For the third assessment, which occurs at 6 months, participants will be given $40 for completion. Finally, after completion of the fourth assessment, which will occur when the baby is 12 months old participants will be given $60. At the 4th assessment, the participant will be given the option of a cash incentive or a gift certificate for a local portrait studio. Therefore, participants can receive up to a total of $160 for completion of all assessments. If additional funding can be secured, and women can be followed up 2-3 years postpartum, an additional $30 will be given for completion of the follow-up assessment which will also consist of an interview and two home visits one-week apart.

Once the main ETS study consent forms have been signed, women will be immediately asked for a saliva sample and will complete a brief past 7 day assessment of cigarette smoking and passive smoke exposure **(See Appendix D: Questionnaires & Assessment Tools).** Salivary cotinine levels will be used to validate self-reported smoking, ETS exposure status, and to stratify mother-infant dyads into the three cohorts. Women will complete the baseline assessment (telephone interview + 2 home visits 7 days apart) within 2-3 weeks of enrollment **(See Appendix D: Questionnaires & Assessment Tools)**. Completion of assessments for women enrolled at 32-35 weeks will take precedence over women enrolled 24-31 weeks due to the limited remaining time for completion of assessments and prenatal intervention sessions (clinic visit and telephone call) prior to delivery. Experiences in Phase II of DCHOPE suggest that this will only be an issue during the first several months of working at a particular clinic. After we are in the field for awhile, we will have already recruited (or missed) women in the later stages of pregnancy and should be present to capture "newly pregnant" women just as they become eligible for ETS (i.e., at 24 weeks gestation).

Successful recruitment/enrollment/retention procedures used in the Phase II DCHOPE study will be applied. In the DC-HOPE study, only 14% of eligible ethnic/gestational age women refused screening. After screening, 85% of women at risk agreed to participate. Only 4% dropped out, 8% were lost to follow-up, and 92% of eligible women completed the postpartum follow-up interview. Retention procedures will include obtaining contact information for women and at least 3 family members/close friends at recruitment, and recording any changes at subsequent measurement follow-ups. This is a standard research procedure, used in our previous studies, to reduce loss to follow-up when women relocate or move during the study. To reduce barriers to continued participation, flexibility of scheduling for both assessment measures and counseling sessions will be emphasized.

Available Population. We anticipate being able to enroll sufficient numbers of women in Cohorts1-3 and, since recruitment will be conducted in conjunction with the NRT study, will maximize recruitment efficiencies. Of 2,550 pregnant women who were approached at these same prenatal clinics in the current DCHOPE study, and who completed ACASI screening, 1,289 (50.5%) were eligible in that they reported having some risk for depression, partner abuse or active/passive smoking. Among those at risk, 1,030 consented to study participation (79.9%). And, among those who were enrolled, 90.9% were at risk because of active or passive smoking. In preliminary analysis of data from African American women enrolled in the previous DCHOPE intervention trial, approximately 48% smoked within 6 months of becoming pregnant, and 43% did not smoke, but were ETS exposed. Of the pre-pregnancy smokers, 29% quit (≤15ng/ml cotinine verified) and 71% continued to smoke as of the baseline interview. At baseline, 62% of the sample reported household cigarette smoke in the past week. Among cotinine verified (≤10ng/ml) non-smoking women with friends or family members who smoke, 77% reported ETS exposure in the past week. The baseline distribution of smoking status/cotinine levels for women in DCHOPE was as follows: 22% Smokers, cotinine >15ng/ml; 12% Spontaneous Quitters, cotinine ≤15ng/ml; 39% ETS Exposed Non-smokers, cotinine ≤10; 2% ETS Exposed Non-Smokers, Cotinine >10 ng/ml and ≤15; and 17% Non-ETS exposed Non-smokers, cotinine

<10ng/ml. Eight percent of women could not be classified into any of these groups. Salivary cotinine assays used in the DCHOPE study were not sensitive below 10ng/ml for detection of ETS, however in this study we will use state-of-the-art procedures enabling detection at levels ≤ 5ng/ml for mothers who smoke, and more sensitive analyses of infant urine.

D.5. ETS Study Intervention Description.

This study will test a clinic-based behavioral counseling intervention (with supplemental telephone contacts) to prevent infant ETS exposure. Clinic-based sessions will be delivered during the immediate prenatal and postpartum visits, and at 2 additional postpartum visits timed to coincide with recommended well-baby visits during the first 6 months postpartum. The schedule for intervention sessions and assessments is presented in Figure 1.

Each clinic intervention session will last approximately 20-30 minutes, although the first visit may last a little longer. The first face-to-face clinic session will be delivered during the prenatal period prior to delivery, the second at 6 weeks postpartum, and the 3-4th sessions will occur at 4, and 6 months postpartum respectively. Face-to-face sessions will be supplemented by four, 5-10-minute telephone counseling calls following each face-to-face visit; one prior to delivery, one at 2 weeks postpartum, and one each at months 3 and 5 postpartum to follow-up on plans, reinforce progress and present biomarker feedback **(Figure 1).**

Figure 1. Display of Assessment and Intervention Contacts.

	Pre-Natal (PN)			Months Postpartum (PP)												
	24-35 Weeks[a]			1[b]	2[c]	3	4	5	6	7	8	9[e]	10	11	12	13
Home Visit Assessment	O					O			O						O	
Telephone Assessment	O					O			O						O	
Delivery & Rescreening Call				O												
Medical Chart Abstractions						O										O
Clinic Session (E/C)		X			X		X		X							
Telephone Session (E/C)			X	X		X		X								
Intervention Check-In Call												X[e]				
Clinic Feedback Visit																X[f]

[a] *Changed recruitment window. The first clinic visit and the prenatal telephone call will occur anytime after recruitment, enrollment and completion of the baseline assessment, but prior to delivery.* [b] *At two weeks*

postpartum, a delivery and rescreening assessment will occur by telephone. [c] *The six weeks postpartum clinic visit will still occur, but the 6-week assessments have been moved back to 3-months postpartum.* [d] *The Infant Health Advisors will call women at 9 months postpartum to check-in to see how they are doing, and to see if they have moved and make sure contact information is up-to-date.* [f] *After the 12-month assessments are completed, the Infant Health Advisors will call women and invite them back to the clinic to receive feedback from the assessments; information and feedback will be provided on social-emotional development from the telephone assessment, and on either ETS or safety hazards levels from the home visit assessments (depending on their intervention group assignment). .*

Experimental Group Intervention Description. This theory-based ETS intervention will focus primarily on prevention of infant ETS exposure, and postpartum relapse prevention (for women who are in Cohort 2), rather than targeting maternal smoking cessation as has been done in several of the briefer, physician-based interventions. That is not to say that smoking cessation will not be discussed, since this is obviously the most effective way of reducing ETS exposure. Rather, we will acknowledge and emphasize the full range of options for infant ETS exposure prevention with mothers and families. Smoking cessation and maintenance will be discussed in the ETS intervention group sessions, since it may contribute to infant ETS exposure. The ETS intervention in Cohort 2 will focus on prevention of postpartum relapse, and mothers in Cohort 1 will be encouraged to quit. Thus, our focus on prevention of ETS exposure may offer a means of effecting harm reduction for infants, and contribute to environmental changes that promote or sustain cessation.

The intervention content and behavioral change methods will be modeled after the current DCHOPE study passive smoke prevention intervention, [66] which integrates Stage of Change [113] and Social Learning Theory (SLT) models **(see Appendix A: Attachments B-E)** . [114] Results recently presented at the Pediatric Academic Society meeting (Blake, et al., 2005; **see Appendix A, Attachment F**) suggest that the DCHOPE intervention was successful in reducing environmental tobacco smoke exposure between baseline and the end of the prenatal assessment interval. Baseline to postpartum reductions in ETS exposure were less apparent, presumably due to the primary intervention focus on reducing passive smoke exposure prior to delivery. In preliminary discussions, the DCHOPE intervention appears to be quite similar in approach to the successful ETS interventions designed by Dr. Hovell and colleagues (**see Appendix A, Attachment G**), also based on SLT, but perhaps with a stronger emphasis on shaping and Behavioral Ecological models [111]. It is expected that a theory-based intervention, focused on infant ETS exposure prevention which combines these two approaches, may facilitate greater success. Logic models and intervention content by session for the ETS Intervention and the control group development and safety intervention are presented in **Appendix A, Attachments H & I**.

The ETS intervention offers the opportunity to test the efficacy of a combination of strategies in the prevention of ETS exposure during infancy. In the current DCHOPE intervention, this includes promoting adoption and enforcement of smoke free infant and household rules, removal of the infant from smokers or smoke-filled rooms, and use of other environmental control/stimulus cue strategies (no smoking signs, remove ashtrays). Mothers will be taught skills in successful communication and negotiation, and be encouraged to reinforce themselves and others for ETS changes. During the intervention sessions, women will be encouraged to identify up to five significant others (e.g., their partner, friends, housemates, or family members) who they believe might serve as supports or advocates to them as they try to reduce ETS or tobacco smoke product use in their homes or elsewhere. And, since the cooperation of significant others is so critical, but <u>only with a woman's permission</u>, informational brochures and other materials about the risks of ETS exposure will be distributed to selected partners, friends and family members in this study. These same partners, friends and other family members will be encouraged to participate, and may be called on the phone during intervention visits, again <u>only with a woman's permission</u>, to enlist their support in helping women find ways to reduce infant ETS exposure and to create tobacco free homes, as well as ways to increase and sustain their support for participating women. It should be noted that significant others are not participants in the study, and they will not complete any research-related assessments. Women struggling with relapse will be encouraged to avoid smoking triggers (e.g., alcohol/other substances, other smokers), taught skills to reduce stress, increase social supports and healthier alternatives. All women will receive support and reinforcement during counseling sessions for progress toward infant ETS exposure prevention objectives, and will receive regular feedback on ETS biomarker results. If efficacious, this will be the first intervention of which we are aware to simultaneously address prevention of infant ETS exposure and postpartum relapse, and it will provide justification for additional testing of more abbreviated sessions in prenatal and pediatric clinic settings.

Household rules against smoking at all in homes can significantly reduce infant and child exposure as measured by urine cotinine to ETS in homes (Berman, Wong, et al., 2003; Blackburn, Spencer, et al., 2003). Early establishment of household rules against smoking during pregnancy appears to be important for ensuring sustained infant ETS avoidance over time postpartum (Sockrider, Hudmon, et al., 2003). Factors associated among women enrolled at 28 weeks of pregnancy who reported having a household policy against smoking in the home at 6 and 12 months included (a) having a policy in effect at the previous assessment, (b) confidence in limiting infant ETS exposure in the home, and (c) perceived difficulty in preventing exposure (Sockrider, Hudmon, et al., 2003). However, research also suggests that household rules or policies need to be absolute; meaning that no smoking at all within homes should be promoted over designated smoking rooms as the best strategy, since there is strong evidence that “designated” smoking areas within restaurants, airports or households provide, at best, only partial protection from ETS exposure through ambient air that easily transfers nicotine to adjacent non-smoking areas (Cains, Cannata, et al., 2004; Pion & Givel, 2004). Thus, the intervention will promote early establishment of household rules against smoking, and will seek to increase confidence and reduce barriers to women being able to prevent ETS exposure in the home.

There is growing evidence to suggest that ETS exposure occurs not only through ambient air, but through direct contact exposures to surface areas within smoking areas such as carpets, furniture and other surfaces (Matt, Quintana, et al., 2004; Van Loy, Riley, et al., 2001; Willers, Hein, et al., 2004). In a recently published study, it was found that infants of smokers are at risk of ETS exposure in their homes through dust, surfaces, and air (Matt, Quintana, et al., 2004). ETS contamination as measured by nicotine in household dust, indoor air, and on household surfaces and infant ETS exposure as measured by continine levels in infant urine were 3-8 times higher in households of smokers who exposed their infants to ETS by smoking indoors than in households of smokers trying to protect their children by smoking outdoors, and 5-7 times higher in households of smokers trying to protect their infants by smoking outdoors than in households of non-smokers (Matt, Quintana, et al., 2004). These findings combined suggest that the intervention will need to address myriad sources of potential contaminants to prevent environmental tobacco exposure among infants.

For the same reasons, women in the intervention group will be advised against smoking or exposure to ETS while they are breastfeeding since increased nicotine concentrations are found in breastmilk (Dahlstrom, Ebersjo, et al., 2004; Stephans and Wilkerson, 1993), and urine continine values from breast-fed babies increases with higher concentrations of cotinine or nicotine in the mothers milk (Dahlstrom, Ebersjo, et al., 2004; Labrecque, Marcoux, et al., 1989; Woodward, Grgurinovich, et al., 1996). Concentrations of nicotine and cotinine are substantially increased among infants of women who breastfeed and smoke (Becker, Manfreda, et al., 1999; Dahlstrom, Ebersjo, et al., 2004; Schulte-Hobein, Schwartz-Bickenbach, et al., 1992; Woodward, Grgurinovich, et al., 1986); according to one study, urinary cotinine excretion was in the range of adult smokers (Schulte-Hobein, Schwartz-Bickenbach, et al., 1992; Woodward, Grgurinovich, et al., 1986). Associations were weaker among infants of smoking mothers who were fed by both breast milk and bottle-fed (Woodward, Grgurinovich, et al., 1986). Detectable levels have also been found among infants of women who breastfeed and are passively exposed, although those concentrations were less evident (Schulte-Hobein, Schwartz-Bickenbach, et al., 1992).

Thus, our definition of environmental tobacco smoke exposure has been expanded from the previous DCHOPE intervention to include all sources of exposure which in aggregate constitute the surrounding environment. This shift means that our intervention will focus on prevention of infant exposure to "environmental" tobacco smoke through ambient air exposures (Berman, Wong, et al., 2003; Blackburn, Spencer, et al., 2003; Sockrider, Hudmon, et al., 2003), breastfeeding (Dahlstrom, Ebersjo, et al., 2004; Labrecque, Marcoux, et al., 1989; Woodward, Grgurinovich, et al., 1996), as well as through other potential ETS exposure sources such as nicotine in dust, or on other surface areas in the home (Matt, Quintana, et al., 2004; Van Loy, Riley, et al., 2001; Willers, Hein, et al., 2004).

Control Group Intervention Description. Women in the control group will receive counseling during a similar number of clinic-based and telephone sessions focused on building parent understanding and skills related to child safety (falls, choking, suffocation, back to sleep, car seats), responsive care giving (e.g., establishing routines, proper supervision) and infant development (developmental milestones, age-appropriate educational play, infant stimulation).

Both Experimental and Control Group Interventions. All intervention sessions (face-to-face and telephone sessions) with women in both groups will include a "clinical assessment interview" to support the coaching process as was done in the interventions for DCHOPE and by Dr. Hovell and colleagues. This assessment will provide information to the counselor from which shaping and tailoring of intervention content can be based. It is not a research assessment, and is therefore not included in Appendix D with other study measures, but rather it is a part of the intervention.

D.6. Staff Training and Quality Control. Infant Health Advisors (IHA's) and Research Assistants (RA's) will be trained using procedures and materials adapted from RTI training protocols for the Phase II, DCHOPE Recruitment Specialists and CNMC Interviewers. Recruitment and data collection monitoring protocols will be implemented to ensure that study recruitment, enrollment rates, and assessment measures are occurring as scheduled, and women are not lost to follow-up. Additional training, quality control, and tracking procedures will be implemented for the home visit assessments. Infant Health Advisors (IHA's) will be trained using procedures and materials adapted from the DCHOPE passive/active smoke intervention training; 3-5 days of training are expected prior to intervention implementation. Regular (weekly/bi-weekly) supervision sessions will occur during the first year of the study, and may be reduced thereafter. Use of case review meetings will be important in monitoring intervention progress, will facilitate IHA's learning from one another, and also help the investigators in early identification of any problems or issues warranting immediate attention. Dr's. Blake, and Katz, who are licensed clinical psychologists, will lead case review sessions related to the ETS study, and shape refinements among counseling staff in consultation with Dr. Hovell as necessary. IHA's will be asked to tape-record sessions periodically with a woman's permission for transcription and supervisory review. Tape recording of sessions is included in the ETS study consent forms.

D.7. Study Process, Impact and Outcome Measures.

D.7.1. Process Evaluation Measures. Process evaluation measures will monitor intervention implementation and fidelity, subject participation (e.g., attendance, drop-out, etc.), as well as the extent to which assessment protocols are being implemented as prescribed. Process evaluation measures will document the flow of procedures and activities, and the degree to which counseling was delivered as intended; documenting client participation in both intervention and assessment procedures, as well as drop out and loss to follow-up. Feedback from process evaluation measures will be provided to inform investigators regarding ongoing study progress. Additionally, process evaluation measures will enable a determination of dose-response relationships in secondary analysis of intervention effects. In collecting process evaluation data, efforts will be made to simultaneously measure, address and eliminate any barriers to study participation during the study pilot-test and initial implementation phases.

D.7.2. Intervention Study Impact Measures. Maternal salivary cotinine assessments will be conducted immediately following prenatal enrollment to verify self-reports, and determine cohort status. Maternal telephone interviews will be conducted at baseline (within 1 month of enrollment), and at 3, 6, and 12 months postpartum. Household ambient nicotine assessments and maternal saliva cotinine will be collected during home visits scheduled at baseline (within 1 month of enrollment), and at 3, 6 and 12 months postpartum. Infant urine cotinine will be collected at the 3, 6 and 12 month postpartum home visits. Infant urine, household ambient nicotine, and maternal reports of infant ETS exposure will occur simultaneously. The assessment schedule was previously shown in Figure 1.

Maternal, Family & Infant Health Information. A family medical history[1] of eczema, allergies, atopy, asthma, chronic bronchitis and other respiratory diseases, and sudden infant death syndrome will be collected at the prenatal baseline interview.

Tobacco Use and ETS Exposure Information. Information will be collected from mothers at each assessment interval on maternal smoking levels, addiction levels (at baseline only), and ETS exposure levels during and after pregnancy, other household or caregiver[2] smoking, changes in smoking status (such as personal attempts to quit or addition of household members who smoke), or changes in household smoking rules and the range of ETS avoidance strategies attempted. At baseline, maternal reports of cigarette smoking and ETS exposure levels will include retrospective reports for each trimester of pregnancy, as well as current levels.

Mediators/Moderators of Maternal Relapse, Child ETS Exposure and Health Outcomes. Assessments of factors associated with maternal smoking cessation and household ETS prevention will include perceptions of the harmful effects of tobacco use and ETS exposure, maternal self-efficacy, motivation to protect her child from ETS exposure, outcome expectations, and social support from others since significant others (particularly partners) can influence intervention success [39, 42]. Other important factors to assess include maternal breastfeeding, formula feeding, weight gain, stressful life events, and maternal depression. Mediators/moderators of child health outcomes will include health beliefs, health care access (e.g., transportation, insurance), utilization, child temperament, home safety and parenting practices [115].

Breastfeeding is particularly important to assess, and to control for in our analyses. As stated earlier, strong associations have been found between breastfeeding and infant urine contine levels. Previous research suggests that if women who smoke or are passively exposed to cigarette smoke breastfeed, it is highly likely that nicotine and cotinine will be passed through the breast milk to the infant, and that those concentrations will in fact be higher than for women who are similarly exposed to tobacco smoke products, but who do not breastfeed (Becker, Manfreda, et al., 1999; Dahlstrom, Ebersjo, et al., 2004; Labrecque, Marcoux, et al., 1989; Schulte-Hobein, Schwartz-Bickenbach, et al., 1992; Woodward, Grgurinovich, et al., 1996).

As will be demonstrated in the next tables, breastfeeding rates among the DCHOPE Phase II sample of African American women were relatively low, the duration of breastfeeding was short,

[1] First degree relatives of the child only.

[2] Caregivers are defined as persons caring for the participating infant for at least 8 hours each week. There may be more than one caregiver.

and few women breastfed exclusively. Furthermore, breastfeeding and duration of breastfeeding was lowest among women who continued to smoke during their pregnancy. As shown in Table 2, nearly half of the DCHOPE Phase II sample of African American women did not breastfeed at all following delivery (45%), 24% breastfed for 4 or fewer weeks 26% for 5-11 weeks, and only 5% breastfed for 12 or more weeks. These percentages would likely shift upwards, but only slightly, for women breastfeeding 12+ weeks had we not been limited by the time frames for conducting the postpartum interviews. No differences between intervention and usual care groups were found in breastfeeding; suggesting that the randomization was effective.

As suggested earlier by other researchers, cotinine levels were weaker among infants of smoking mothers who were fed by both breast milk and bottle-fed (Woodward, Grgurinovich, et al., 1986). Very few women in the DCHOPE Phase II sample of African American women exclusively breast fed their infants. As shown in Table 3, 71% of the DCHOPE Phase II sample of African American women fed their infant something other than breast milk within the first week postpartum; only 12% waited beyond 5 weeks postpartum to feed their infant something else. Again, no I vs UC differences were found. Thus, exclusive breastfeeding is highly unlikely in this population beyond the first four weeks postpartum.

Table 2. Breastfeeding by Intervention & Usual Care Groups

	I N=391	UC N=401	Total N=792	Significance
Breastfeeding				
Never Breastfed			45%	NA
Breastfed 1-4 weeks			24%	
Breastfed 5-11 weeks			26% [a]	
Breastfed 12+ weeks			5% [a]	
Breastfeeding				
Never Breastfed	45%	46%	45%	NS
Breastfed 1-4 weeks	25%	24%	24%	
Breastfed 5-11 weeks	9%	9%	9%	
Breastfed 12+ weeks	1%	2%	1%	
Still breastfeeding	20%	19%	20%	

[a] Women (20%) who reported they were "still breastfeeding" at the postpartum interview were collapsed into categories based upon the number of weeks postpartum the follow-up interview occurred.

Table 3. Exclusivity of Breastfeeding by Intervention & Usual Care Groups

	I N=391	UC N=401	Total N=792	Significance
Week Postpartum Began Bottle-Feeding				
< 1 week			71% [a]	NA
1-4 weeks			18%	
5-11 weeks			10% [b]	
12+ weeks			1% [b]	
Week Postpartum Began Bottle-Feeding				
< 1 week [a]	67%	74%	71%	NS
1-4 weeks	20%	15%	18%	
5-11 weeks	7%	5%	6%	
12+ weeks	1%	1%	1%	
Only fed breast milk	5%	5%	5%	

[a] Includes women who never breastfed.

[b] Women (5%) who reported at the postpartum interview they had only fed their infant breast milk since delivery were collapsed into categories based upon the number of weeks postpartum the follow-up interview occurred.

An inverse association has been consistently found between maternal smoking and breastfeeding across studies and countries (Amir and Donath, 2003; Donath and Amir, 2004); in nearly all studies to date, women who smoke are less likely to breastfeed. Therefore, we anticipated that women who smoked and chose to breastfeed would be a smaller subset of women. We further looked at data from the DCHOPE Phase II sample of African American women in two ways; first, based on whether women had smoked a cigarette since delivery (Table 4), and second, based upon their smoking status at ACASI screening (Table 5). Twenty-four percent of the sample reported having smoked at least one cigarette since delivery, 33% reported exposure to passive smoke in the past 7 days, and 43% reported no exposure to passive smoke in the past 7 days. Consistent with our expectations, women who reported having smoked since delivery were significantly less likely to breastfeed, or to sustain breastfeeding beyond 5 weeks postpartum; only 18% had done so compared with 29% of women who reported passive smoke exposure, and 40% of women who reported not having smoked since delivery and no recent passive exposure. Similarly, smokers and those passively exposed were more likely to initiate bottle feeding within the first four weeks postpartum.

Table 4. Breastfeeding and Exclusivity of Breastfeeding by Smoking Status Since Delivery

	Active [a] N=190	Passive [b] N=257	Neither [c] N=341	Total N=788	*P*-Value
Breastfeeding					
Never Breastfed	56%	45%	40%	45%	.0001
Breastfed 1-4 weeks	26%	27%	21%	24%	
Breastfed 5-11 weeks	9%	11%	8%	9%	
Breastfed 12+ weeks	1%	2%	1%	1%	
Still breastfeeding	8%	16%	29%	20%	
Week Postpartum Began Bottle-Feeding					
< 1 week [a]	79%	73%	65%	71%	.05
1-4 weeks	14%	16%	20%	17%	
5-11 weeks	4%	6%	7%	6%	
12+ weeks	0%	< 1%	1%	1%	
Only fed breast milk	3%	5%	7%	5%	

[a] Active smoke refers to women (24%) who reported they had smoked at least one cigarette since delivery.

[b] Passive smoke refers to women (33%) who reported they had NOT smoked a cigarette since delivery, but who were exposed to a cigarette in the past 7 days.

[c] Neither refers to women who did not report either of the above (43%).

Results were similar for African American women who screened into the study as Active (46%), Passive (45%) or Neither (9%). As shown in Table 5, women who were pre-pregnancy smokers were significantly less likely to breastfeed, or to sustain breastfeeding beyond 5 or more weeks postpartum; only 24% of the smokers had done so, compared with 34% of women who reported passive smoke exposure, and 53% of women who reported no smoking or passive smoke exposure on the ACASI screener. Women who were classified as smokers on the ACASI-screener were no more or less likely to initiate bottle feeding within the first week postpartum than the two other groups.

Table 5. Breastfeeding and Exclusivity of Breastfeeding by Smoking Status At Recruitment

	Active [a] N=361	Passive [b] N=358	Neither [c] N=69	Total N=788	*P*-Value
Breastfeeding					
Never Breastfed	51%	43%	26%	45%	.0001
Breastfed 1-4 weeks	25%	24%	22%	24%	
Breastfed 5-11 weeks	9%	9%	12%	9%	
Breastfed 12+ weeks	1%	2%	3%	1%	
Still breastfeeding	14%	23%	38%	20%	
Week Postpartum Began Bottle-Feeding					
< 1 week [a]	75%	69%	58%	71%	NS
1-4 weeks	15%	18%	28%	18%	
5-11 weeks	6%	6%	9%	6%	
12+ weeks	<1%	1%	1%	1%	
Only fed breast milk	4%	6%	4%	5%	

[a] Active smoke refers to women (46%) who reported they had smoked at least one cigarette in the 6 months prior to becoming pregnant on the ACASI screener.

[b] Passive smoke refers to women (45%) who reported they had NOT smoked a cigarette in the 6 months prior to becoming pregnant, but who were passively exposed to cigarette since becoming pregnant on the ACASI screener.

[c] Neither refers to women who did not report either of the above on ACASI screening (9%).

Results presented above for women in DCHOPE appear to be comparable to those reported nationally as part of the Healthy People 2010 progress reports for the percentage of African American women who breastfed early postpartum in both 1998 and in 2001 (55% for DCHOPE vs. 45% for African American women in 1998, and 53% in 2001). *Healthy People 2010* set the target of 75 percent for new mothers breastfeeding in the hospital, 50 percent maintaining breastfeeding for at least 6 months, and 25 percent continuing for 1 year (USDHHS, 2000). In 1998 (Abbott Laboratories, 1999), about 45% of African American women breastfed during the early postpartum period following delivery; only 19% continued 6 months postpartum and 9% were breastfeeding at 12 months, compared to white women (68%, 31% and 17% respectively). In 2001, breastfeeding rates were the highest recorded since national breastfeeding data have been collected. The initiation rate or in-hospital breastfeeding rate was 69.5 percent for all women. This rate increased most among groups of mothers that have traditionally been the least likely to breastfeed, Black and Hispanic women. In 2001, 52.9 percent of Black women and 73 percent of Hispanic women initiated breastfeeding in the hospital. In fact, 2001 was the first year that the highest in-hospital breastfeeding rates were among Hispanic women

(USDHHS, 2000).

D.7.3. ETS Intervention Group Study Outcomes. The ***primary outcome*** for the ETS intervention study is infant ETS exposure. The two primary outcome measures of infant ETS exposure for the ETS intervention are: 1) maternal reports of infant ETS exposure at home and elsewhere, and 2) infant urinary cotinine levels. It is anticipated that maternal reports of ETS exposure, and infant urinary cotinine levels will increase more among the control families compared to those in the experimental condition over time. Most studies recommend collecting both maternal reports and biomarkers to assess passive smoke exposure, and outcomes in ETS intervention studies. ***Secondary outcomes*** include 1) household ETS exposure levels as measured by ambient air nicotine levels, and 2) maternal salivary cotinine levels which will be used to confirm self-reported cigarette smoking, postpartum relapse and maternal ETS exposure levels.

Maternal Reports of Infant ETS Exposure. Maternal reports of infant ETS exposure (primary outcome for the ETS intervention) at home and in other sites regularly visited by the child [3] will be collected at all postpartum assessments. Strong evidence exists in the literature to suggest that mothers can provide reliable and valid reports of their infant or child's ETS exposure [107]. Strong concordance between maternal reports of infant (beginning at age 3 months) and child ETS exposure and child urinary cotinine levels exist, particularly when parents are reporting their own tobacco use as opposed to the use of tobacco by other household members [108, 116].
Infant ETS exposure at home will be derived from maternal reports of infant exposure during telephone interviews and home visits. During telephone interviews, mothers will report the number of cigarettes smoked within the home on a typical day in the past 7 days, and the number of those cigarettes to which the infant is exposed postpartum. A summary score will be derived by multiplying the number of days smoking occurred in the home by the number of cigarettes smoked around the infant on a typical day. During the home visit (at the time when the nicotine air monitors and infant urine are collected), mothers will be asked to enumerate infant exposure to cigarette smoking for each day of the past seven days, rather than relying on a typical day and multiplying by seven as is being done with data from the telephone interviews. Maternal reports of infant and child ETS exposure within the previous 7 day period are commonly used in the literature. Most studies have used 7 day recall periods, although some

[3] These will be included if the child spends at least 8 hours each week at the site. There may be more than one site.

studies have used shorter recall intervals (e.g., 3 day intervals; Daly, Wiggers, Considine, 2001).

Measurement of Infant Cotinine Levels. Infant urine cotinine levels will be the second primary outcome for the ETS intervention [90, 117, 118]. Infant cotinine levels will be measured in urine collected from diapers, and analyzed using state-of-the art mass spectrometry with a limit of detection of less than 50 parts per trillion (0.05 ng/ml). Infant urine will be collected during the home visits to validate maternal reports of ETS exposure, and measure reductions in infant ETS exposure levels over time. The half life of cotinine in children is longer than for adults (Jaakkola and Jaakkola, 1997), and potentially detectable up to 72 hours or longer in younger children or infants as compared to 20 hours for adults (Collier et al., 1994).

Analysis of infant urinary cotinine levels has varied in previous studies. Infant or child ETS exposure levels based upon urinary cotinine have been reported as 1) mean infant urine cotinine levels, 2) mean infant urine cotinine/creatinine ratios which correct for dilution in urine (Haufroid and Lison, 1998), or 3) using a dichotomous variable (e.g., a cut-off point to reflect ETS exposure (Yes/No) that is derived from the mean cotinine level or the continine/creatinine ratio. Previously used cut-off points to differentiate unexposed and exposed to ETS infants and children have included the following: $\leq$ 1.0 ng/mL in urine cotinine as verification of no smoke exposure (=0) and > 1.0 as evidence of exposure since the range in homes where no smoking occurs is (range = 0.6 to 1.8 ng/mL) (Hovell, Meltzer, Wahlgren, et al., 2002), adjusted urine cotinine levels of > 5 ng/mg (adjusted for creatinine) (Cornelius, Goldschmidt, and Dempsey 2003), urine cotinine/creatinine ratios (CCR) (30 ng/mg cotinine-creatinine) (Henderson, Reid, Morris, et al., 1989), 10 ng continine per mg creatinine in urine (Bakoula and Kafritsa, 1995; Chilmonczyk, Salmun, Megathlin, et al, 1993), 10 ng/mL cotinine (as an uptake marker of nicotine with log transformed mean values to normalize distributions and equalize variances, and where transformed means were exponentiated to obtain geometric means) (Sexton, Adgate, Church, Hecht, et al., 2004), and 30 ng/mg of cotinine (adjusted for creatinine) (Seifert, Ross, and Norris, 2002). Other investigators have used the mean log ratio of the follow-up to initial urine cotinine measurement (Chilmonczyk, Palomaki, Knight, Williams, and Haddow, 1992), mean urinary cotinine to creatinine ratios (which are then transformed using logarithmic e transformation and recorded as geometric means since they are not normally distributed (Blackburn, Spencer, Bonas, Coe, et al., 2005), and geometric mean urine cotinine levels (Hovell, Meltzer, Wahlgren, et al., 2002).

In this study, we will use either mean cotinine levels or a cut-off point established within our population of African American and Hispanic infants, because cotinine levels tend to vary by ethnic/racial groups (England, Kendrick, Gargiullo, et al., 2001; Sexton, Adgate, Church, Hecht, et al., 2004). The final variables that will be used in our data analysis will depend upon the distribution of data collected, and in consultation with collaborating expert statisticians and advisors.

Measurement of Maternal Cotinine Levels. Maternal salivary cotinine will be collected at the same time as the collection of the nicotine monitors and infant urine, as well as self-report information, preferably within 24 hours of completion of the ambient nicotine monitoring, and analyzed using radioimunnoassay (RIA). Salivary cotinine levels of $\leq$17 ng/ml, found to maximize sensitivity and specificity in a receiver operating characteristic (ROC) curve in our previous DCHOPE sample, [64] will confirm maternal cessation or relapse (a secondary outcome).

Maternal salivary cotinine will be collected, and first analyzed using radioimunnoassay (RIA) to detect levels of tobacco smoke exposure. The Immulite 1000, that was recently purchased by study investigators at GWU, will be used by Dr. David Perry to complete cotinine analyses for women who smoke in both the ETS and NRT studies. Cotinine samples that are found to fall below the lower limits of detection of the Immulite 1000 at GWU will be sent off for further analysis by LC Tandem Mass Spec (LC-MS), which enables detection sensitivities down to 0.05 ng/ml, and is very important since passive smoker levels can be found in the range of 0.05 to 1.0 ng/ml.

Assuming we can show in our pilot study analysis of the split-half samples that the two saliva cotinine measure values are similar at higher levels (e.g., > 5 or 10 ng/ml), and we can determine where the lower detection limits are for the Immulite 1000 (e.g., perhaps the Immulite can detect as low as 5 ng/ml reliably), then it would definitely be worthwhile to only send samples out for LC-MS analysis from women whose values are at the lower limits of detection for the Immulite 1000 (Neal Benowitz, personal communication, June 2005). And, because we will have completed the preliminary split-half test samples during our pilot study, and assuming we determine that the analyses using the two methods are similar, then it is very reasonable and defensible to use saliva data analyzed these two ways simultaneously in analyses – since the values would essentially be equivalent either way. The data can be combined, and will not affect mean values reported (Neal Benowitz, personal communication, June 2005).

Maternal reports of having smoked at all within the previous seven days as determined by 1) self-reported smoking levels in the past 7 days during telephone interviews (e.g., of the number of days smoked and the number of cigarettes smoked per typical day in the past 7 days), and 2) past 7 day smoking levels as reported on the Tobacco Smoke Questionnaire which is used when collecting saliva samples, will be combined with maternal salivary cotinine levels to determine whether women continue to smoke. Maternal reports of having smoked at all within the previous seven days or having a cotinine value that exceeds established cut-off points for cigarette smoking will determine whether a woman is a current smoker or non-smoker.

In previous studies, maternal reports of cigarette smoking have been generally derived from having smoked a cigarette at all in the past 7 days (Boyd, et al., 1998; England, et al., 2001a; England, et al., 2001b; Ershoff, et al., 1999; Melvin, et al., 2000). Salivary cotinine cut-off points in previous intervention studies with pregnant women have included salivary cotinine levels of 30 ng/ml (Boyd, et al., 1998; Hegaard, et al., 2003; Melvin, et al., 2000), or 20 ng/ml (Ockene, et al., 2002). A ROC curve derived cut-off point of 24 ng/ml maximized sensitivity and specificity (Boyd & Windsor, 1998): while a cut-off point for blacks of 25 ng/ml, and 11 ng/ml for whites was reported (Boyd, Windsor, Perkins, Lowe, 1998). The cigarette smoking cut-off point that maximized sensitivity/specificity in ROC curves for our population of African American women participating in the DCHOPE Phase II study was 17 ng/ml (Blake, et al., unpublished data, 2005; see **Appendix A; Attachment F**).

In this study, analysis of point prevalence abstinence based on self-report and verified by cotinine levels, and mean cigarette smoking levels (from self-report) and salivary cotinine levels will be used to assess intervention effects. Point prevalence abstinence for maternal cigarette smoking will be determined in 2 ways: 1) based upon established cut-off points in the literature (e.g., in studies of pregnant and postpartum women), and 2) a population-specific ROC curve for women participating in this study. Sustained abstinence or cessation postpartum will be determined based on cumulative point prevalence abstinence rates across all postpartum intervals.

Maternal ETS exposure levels will be similarly measured by maternal salivary cotinine levels combined with 1) self-reported ETS exposure levels in the past 7 days (e.g., of the number of days exposed, and the typical number of cigarettes exposed to per day in the past 7 days at home and away from home). The ROC curve derived cut-off points for evidence of maternal ETS exposure levels will be based on other studies in the literature. Traditionally, salivary cotinine levels > 5ng/ml is considered reflective of passive smoke exposure, with heavy passive exposure resulting in levels greater than or equal to 10 ng/ml (Etz, 1990), and below the established cut-off point for actual cigarette smoking, have been considered representative of ETS exposure. Levels of exposure are detectable at lower levels today (Mannino, Caraballo, Benowitz, Repace, 2001). The TSP exposure cut-off point that maximized sensitivity/specificity in ROC curves for our population of African American women participating in DCHOPE Phase II was 10 ng/ml (Blake, et al., unpublished data, 2005; see **Appendix A, Attachment F**). These cut-off points were due to the fact that lower limits of detection for the laboratory used for the DCHOPE Phase II analysis was 10 ng/ml using GC analysis whereas lower limits of detection for LCMS methods are at 0.05ng/ml (and above which individuals are considered to have been ETS exposed).

Household Ambient Nicotine Monitors. While not a precise measure of infant nicotine exposure, ambient nicotine monitors will be used to measure ETS levels in the home; for cost reasons, we will rely on maternal reports of ETS exposure outside the home. Ambient nicotine levels are an additional secondary outcome of the ETS intervention.

Trained RA's will visit participant homes to place a nicotine monitor in the room where the infant spends the greatest amount of time and/or where the greatest ETS exposure is reported for the infant. The monitors will remain in the home for 7 days, and then will be picked up by the RA. Ambient air nicotine monitors and analysis procedures, as described by Hammond, [119] will be used. Nicotine air monitors will be collected during home visits simultaneous with collection of infant urine cotinine and maternal reports of infant ETS exposure from diaries. Monitors will be sent to Johns Hopkins University for analysis.

Household nicotine levels (as measured by ambient nicotine monitors in the home) will be used to assess household smoking levels and to validate maternal reports of household smoking. Ambient nicotine levels at baseline, 4-6 weeks, 6 and 12-month postpartum will be used to assess change in the infants' (and all family members') residential exposure to ETS. Household ETS exposure has previously been defined as point prevalence abstinence (Emmons, Hammond, Fava, Velicer et al., 2001), or has been used as a continuous variable (Henderson, Reid, Morris, et al., 1989; Hovell, Meltzer, Zakarian, et al., 1994; Matt, Quintana, Hovell, Bernert, et al., 2004), and over varying assessment time durations: two weeks (Hovell, Meltzer, Zakarian, et al., 1994), seven days (Emmons, Hammond, Fava, Velicer et al., 2001; Matt, Quintana, Hovell, Bernert, et al., 2004), two days (Henderson, Reid, Morris, et al., 1989).

Results will be presented as the ratio of nicotine concentration to the number of hours monitored (i.e., the number hours dosimeters are in use).

D.7.4. ETS Control Group Study Outcomes. Since the control group in the above ETS intervention study will receive a similar amount of intervention time, or attention, and those mothers will in fact receive an intervention focused on prevention of safety hazards and promotion of child development, there will be certain assessments conducted at each measurement interval that will focus specifically on these issues; parenting supervision practices, parent routines (e.g., for feeding, sleeping), infant stimulation, parent-child interactions, knowledge of safety hazards, and observations to assess the presence or absence of safety hazards in the home. Child competence, a secondary outcome of the child development intervention, will additionally be assessed using a standardized scale at 12 months only [120, 121].

In assessing both the ETS and child safety/development intervention outcomes at each interval, we will make sure that our assessment staff are not aware of which intervention a woman is receiving. Research assistants and home visitors will be "blinded", to the extent possible, as to the intervention assignment of each woman. It is certainly possible that they may ascertain a woman's intervention group status during the assessment process, but such questions will be discouraged during training, and no affirmations of a woman's intervention status will be given by study investigators.

D.7.5. Child Health Study Outcomes. At each postpartum assessment, mothers will be asked to recall information about infant health; all major and minor illnesses and complaints, all adverse health events, and health care utilization or hospitalizations for the proceeding interval (e.g., birth to 3 months, 3 months to 6 months, and 6 months to 12 months). Previously validated chart abstraction methods will be used to collect infant health information after the 12 month follow-up.[96]

Maternal Reports of Illness. Indices of health problems to be assessed at each interval will include frequency and severity of colds, ear infections, bronchitis, pneumonia, asthma, wheezing, rattling in the chest, persistent coughing, or breathing difficulties, and any other respiratory illnesses. Additionally, the incidence of fevers. eczema, colic, diaper rash, spitting up or reflux, vomiting, diarrhea, constipation, anemia, and other types of feeding problems, problems sleeping, immunization reactions or allergies to food, milk or formula will be assessed. For each illness, mothers will be asked 1) whether that illness occurred during the previous interval, and if so, 2) how often during the previous interval it occurred (e.g., 1, 2, 3, 4 or more times). Additionally, mothers will be asked whether there were any illness-related doctor's visits, emergency room visits or hospitalizations for any of the above illnesses since the last interview.

Medical Records Abstractions. The frequency and severity of all types of illnesses, as well as any illness-related doctor's visits, emergency room usage, or hospitalizations for any of the above illnesses, will also be collected through medical chart review of infants and mothers immediately postpartum, and for infants following the 12 month follow-up assessment.

The majority of previous studies have compared the effects of ETS exposure on older children, as opposed to infants, and more often than not, looked only at one or two specific health outcomes (e.g., wheezing, ear infections) as opposed to the full range of health outcomes being assessed in this study. Therefore, incidence of <u>all</u> discrete health events of interest over the first year of life will be the dependent measure to assess health outcomes (<u>exploratory and secondary outcome</u>).

Summary scores overall and within 3 categories of illnesses (e.g., respiratory, gastrointestinal, other) more or less likely to be affected by ETS exposure will be calculated to yield a count of the number of different types of illnesses within the preceding interval (count of "Yes" responses), as well as the overall frequency of occurrence (e.g., a summary score of the frequency as reflected by a sum of times each occurred; 0+1+2, etc.). To control for variations in the length of assessment intervals, summary scores may be adjusted based upon the number of weeks in the preceding interval. Similarly, scores reflecting the frequency of illness-related doctor's visits, emergency room usage, and hospitalizations for any of the above illnesses will be created and serve as an index of illness severity. A 12-month prevalence of persistent illnesses (overall and within specific categories) will also be calculated across the 12 month study period.

D.8. Data Analysis, Sample Size & Statistical Power.

Data analysis will be performed by the DCHOPE Data Coordinating Center, Research Triangle Institute.

D.8.1 Specific Aim # 1: ETS Intervention Study Outcomes. This aim calls for determining the effects of the intervention on infants' ETS exposure using data collected from Cohorts 1-3. Since women in the intervention group will be encouraged to prevent infant exposure to ETS and postpartum relapse, we hypothesize that infant urine cotinine levels and maternal reports of infant ETS exposure will increase more among the control families compared to those in the experimental condition over time. Similarly, it is expected that household nicotine levels and maternal salivary cotinine levels will increase more among C than E families.

An intention-to-treat model will be used to evaluate intervention effects. Drop-out (4%) and lost to follow-up rates (8%) are low in the current DCHOPE study, however because the intervention is being conducted postpartum, we expect this may be somewhat higher (perhaps as high as 20%). Therefore, we will recruit 375 women to achieve a final sample of n=300 mother-child dyads (150 per E/C group). Sample size justifications follow at the end of this section. A repeated measures design (2-groups; 1-prenatal baseline, 4- postpartum dependent measures), controlling for significant E/C differences at baseline, will be used to test the hypothesis that infant ETS exposure (as measured by infant urine cotinine levels and maternal report) will increase more among C than E families; using the group x time interaction to test for differential rates of change between groups.

A generalized estimating equation (GEE) approach will be employed in the analysis to model the effects of group, time, group by time interactions, the effects of covariates, and to test specific hypotheses. This interaction is important in our repeated measures analyses because we hypothesize that infants and mothers in the intervention group will have different patterns of behavior over time than women in the usual care group. GEE is a multivariate version of generalized linear models and permits a variety of link functions, covariance structures, mean-variance relationships, and correlation structures to be specified.[123] Generalized estimating equations (GEE) enable analysis of missing data, and take into account the fact that repeated measurements taken on the same subject are not independent, but correlated. GEE can be thought of as an extension of logistic regression. In addition, models may include other covariates found at baseline to differ between groups which could influence outcomes of interest. Demographic covariates will be reduced using a backwards selection process with an exit value of $p = 0.20$. Each final model will then be run to obtain odds ratios and individual chi-square tests to compare combinations of care group and time.

We fully recognize the importance of first determining levels of, and exploring reasons for missing data in data sets prior to choosing the best statistical model for both the observed/unobserved data, and we are currently conducting such analyses as part of the Phase II, DCHOPE study. Before conducting analyses, statistical comparisons will be made to investigate the comparability of the intervention and control groups with respect to various background variables in order to determine whether key differences exist between women with and without follow-up at each assessment time point. It is particularly important to determine whether data are missing at random (Chen and Little, 1999). Our approach to analysis thereafter will depend on the levels of missing values, and whether those missing values appear to be occurring at random. Based upon the results of these comparisons and the magnitude of the missing values for the key variables, multiple imputation techniques may be employed to help adjust for potential bias in our outcomes due to this non-random drop-out.

Various strategies have been discussed to address missing data in the adult smoking cessation intervention literature including problems accruing to complete-case analysis, last observation carried forward, mean substitution approaches, and coding participants with missing data as using tobacco (Chen & Little, 1999; Hall, Deluchhi, et al., 2001; Hedeker & Gibbons, 1997).

When there is considerable missing data, Hall et al., (2001) suggest that optimal missing data analysis strategies include a careful description of reasons for data being missing, along with use of either pattern mixture or selection modeling and sensitivity analyses. They suggested that *"If the proportion of missing data is more than 10–20% of the total sample, especially if differential attrition occurs, the method for handling missing data should be identified and justified. Pattern mixture models and selection models should be considered in such instances, along with sensitivity analyses rather than complete-case analysis or coding all missing data as indicative of smoking."* (Hall et al., 2001). Random effects models should be augmented by including variables defined by a subjects pattern of missing data -- pattern-mixture approach (Hedeker and Gibbons, 1997). "Selection models" generally involve two stages that are performed separately or iteratively: 1) a predictive model is developed for whether or not a subject drops out with variables obtained prior to the drop out, and then 2) these drop out propensity scores are used in the second stage, as a covariate to adjust for the potential influence of dropout (Hedeker and Gibbons, 1997). These approaches will be incorporated in the analysis in consultation with RTI statisticians and consulting investigators as appropriate.

In our original protocol, we proposed to either control for breastfeeding in our analyses, or to alternatively use cotinine as an outcome only among non-breastfed infants since breastfeeding might confound infant cotinine levels. After further review of the literature, and in consultation with Dr. Hovell and other study investigators, we have since decided against eliminating infants of mothers who smoke and breastfeed from our analyses. Instead, we will assess I versus C group changes in infant urine cotinine levels with and without levels of breastfeeding as a covariate in our analyses. This decision was made for several reasons: (1) stratified randomization of women based upon a woman's smoking status at baseline into one of three groups (i.e., current smokers, quitters, and women who are only passively exposed) is likely to ensure equal allocation of women who choose to breastfeed postpartum, (2) further review of the literature which suggested variable exposure levels based on the exclusivity of breastfeeding, the distribution of breastfeeding in our sample, and inherent difficulties associated with determining which infants would be eliminated (e.g., infants of women who breastfeed at all, who breastfeed exclusively, or those who breastfeed beyond 4+ weeks which is when our first infant urine sample will be taken), and perhaps most importantly (3) a shift in our original thinking about the definition of "environmental" tobacco smoke exposure. If by definition the "environment" refers to the "circumstances, objects, or conditions by which one is surrounded" and it includes the "complex of physical, chemical, and biotic factors" (www.Merriam-Webster.com), then all sources of exposure will need to be included in our efforts to prevent infant environmental tobacco smoke exposure, since in aggregate they constitute the surrounding environment.

As discussed in Section D.5, this shift means that our intervention will focus on prevention of infant exposure to "environmental" tobacco smoke from all sources: through ambient air exposures (Berman, Wong, et al., 2003; Blackburn, Spencer, et al., 2003; Sockrider, Hudmon, et al., 2003), TSP exposure through breastfeeding (Dahlstrom, Ebersjo, et al., 2004; Labrecque, Marcoux, et al., 1989; Woodward, Grgurinovich, et al., 1996), as well as exposure to other potential ETS exposure sources such as nicotine in dust, or on other surface areas in the home (Matt, Quintana, et al., 2004; Van Loy, Riley, et al., 2001; Willers, Hein, et al., 2004). Women in the intervention group will be encouraged to protect their infant from ETS exposure, to establish no smoking household rules, to clean household surfaces and remove all TSP products and dust, and advised against smoking or becoming exposed to ETS themselves while they are breastfeeding. In so doing, infants that have elevated urine cotinine levels in this study, regardless of the source of "environmental" tobacco smoke, will be considered as having been exposed.

We have based power/sample size estimates on a recent review on the effectiveness of 19 ETS intervention studies published 1987-2002 suggesting that the average effect size (Cohen's d) was .34, with a range from -.14 to 1.04 [31]. We anticipate that 300 mother-child dyads (150 each in the intervention and control groups) will be sufficient to show intervention effects at 6 and 12 months postpartum assuming a significance level (alpha) of 5%, and the probability of the event under consideration (ETS exposure) in the control group is 90% (assuming some errors in measurement of cotinine levels). Based on the information available in the literature for various relative risk (RR) values (relative risk of events, i.e., ETS exposure, in the intervention group relative to those in the control group with RR values in the range 0.33 - 0.95), the probability of rejecting the null hypothesis (that RR=1 when the true RR equals the assumed RR), a RR of at least 0.85 guarantees a power of at least 80% under the above assumptions (alpha=0.05, 150 cases/group, and 90% prevalence of ETS exposure in the control group). We anticipate being able to scale the sample size back to as few as 170 women (n=85 per E/C group), should the study need to be scaled back for budgetary reasons, and still be able to detect significant effects.

D.8.2. Secondary Intervention Study Analyses. We will explore 1) dose-response effects between completion of intervention sessions and infant ETS exposure, 2) maternal relapse rates and smoking levels between I/C groups, and 3) changes in mediating/moderating factors targeted in the E group (e.g., partner or other household member smoking levels, breastfeeding, maternal smoking relapse postpartum) and prevention of infant ETS exposure. Since the Control group will receive a safety/development intervention, we will similarly explore those results as well. Assessments will include standardized/adapted measures reflecting parenting practices (e.g., supervision, routines, protectiveness), home safety knowledge and practices, parent-child interactions at 3, 6, and 12 months, and child social-emotional competence (at 12 months only) using the Brief Infant-Toddler Social and Emotional Assessment (BITSEA).

D.8.3. Exploratory Aim # 2: Infant Health Study Outcomes. As part of our analyses for Exploratory Aim # 2, we will assess infant negative health outcomes associated with levels of TSP/ETS exposures during pregnancy and postpartum. We recognize that it is not the acute level of TSP/ETS exposure that may be a critical determinant of child health outcomes, but cumulative ETS exposure levels over years. This study will not be able to address the issue of prolonged cumulative exposures since 1) we will not be assessing prenatal exposures throughout pregnancy, other than retrospectively, 2) we will not be measuring continuous infant ETS exposure postpartum as our measures are scheduled only three times during the first 12 months, 3) we are not enrolling a non-TSP/ETS exposure group, and our experimental groups will likely not have reduced infant ETS exposure to zero postpartum, and 4) short term follow-ups over the course of the first year of life are not likely to show strong health effects. However, this study will set the stage for future epidemiological studies to assess the health effects of cumulative levels of exposure over longer study intervals.

The intent of this secondary analysis is to estimate the relative risk for all possible ETS-related adverse health outcomes in children based upon ETS (passive exposure) postpartum, maternal smoking and/or ETS exposure during pregnancy (gestational exposure), or both. After adjusting for potential confounders, the relative risk for incidence of adverse health events based on infant history of exposure to TSP in-utero and ETS postpartum (exposed vs. not exposed) will be compared. We anticipate that the relative risk of having an adverse health outcome will be increased among TSP/ETS exposed compared to non-exposed infants; risk will be greatest among infants with combined smoke exposure (prenatal and postpartum) and lowest among those with no exposure (prenatal or postpartum).

We will use both maternal self-reports of prenatal and postpartum TSP/ETS exposure, as well as more precise measures of infant urine cotinine that can detect very small levels of ETS exposure postpartum. Infant urinary cotinine levels measured across the year will be used to stratify infants into ETS-exposed, and minimally or non-exposed groups of infants postpartum (using a cut-off of 10ng cotinine per mg of creatinine in infant urine). Retrospective maternal reports of cigarette smoking and ETS exposure during pregnancy, combined with confirmatory salivary cotinine levels at the baseline prenatal assessment (taken in the 3rd trimester), will enable stratification of infants who were prenatally exposed to TSP in utero at varying levels.

Statistical analysis will follow GEE procedures outlined in Exploratory Aim 2 # above, as well as similar approaches to missing data analyses. This will enable us to assess the association between change in selected health outcome measures and change in ETS exposure, and will permit the introduction of covariates to inform the analysis concerning the specific conditions under which health benefits may or may not be noted. Statistical power appears adequate to enable exploration of hypotheses concerning associations between ETS exposure and health outcomes.

We based power/sample size estimates on previous studies of child health outcomes, however those studies were limited by comparisons of the effects of ETS exposure on older children, as opposed to infants, and more often than not by having included only one or two specific health outcomes, as opposed to the full range of health outcomes being used in this study. In one study looking at extent to which ETS impacted wheezing among 5800 asthmatics, Odds Ratios (OR) differentiating between ETS exposed and unexposed children were fairly low; OR=1.7 for wheezing with colds and OR =1.6 for going to hospital, OR=1.4 for persistent wheeze [20]. In a second study, Lieu and Feinstein [23] found the occurrence of any ear infection was not increased by passive smoke exposure (adjusted risk ratio {RR}, 1.01; 95% confidence interval {CI}, 0.95-1.06), but was slightly increased by gestational age (adjusted RR, 1.08; 95% CI, 1.01-1.14) and combined (adjusted RR, 1.07; 95% CI, 1.00-1.14) smoke exposures. The risk of recurrent ear infections (> or = 6 lifetime episodes) was significantly increased with combined smoke exposure (adjusted RR, 1.44; 95% CI, 1.11-1.81).

Depending on the above distributions, we anticipate that 300 mother-child dyads should be sufficient to explore effects due to prenatal exposure in children under age 1 year. RR should be less than 80% to achieve a power of 80% if we retain only 100 cases per group, and should be less than 75% to achieve a power of 80% if we retain only 75 cases per group. . For a multiple linear regression analysis, assuming N=300, alpha=.05, and a regression equation with as many as 8 independent variables that produces an R-square of .30, power to detected an increase in R square of .05 or more associated with the addition of one more independent variables to the regression is 99%. However, since the distribution of infant ETS exposure has yet to be determined (i.e., the percentage of infants exposed postpartum), it is difficult to know whether a sufficient sample size will be obtained to differentiate between effects due to prenatal tobacco exposure and postnatal ETS exposure. It is our hope that, since we are embedding this study within the context of an intervention, we may be able to identify more mother-infant dyads in which infant exposure only occurs prenatally, and not postpartum.

Additionally, an alternative strategy to exploratory analyses of health outcomes for the E/C groups may parallel analyses used by Greenberg, Strecher, Bauman, et al. (1994) in an intervention study. [5] In the Greenberg et al. (1994) study [5], the investigators assessed the significance of differences in acute lower respiratory illnesses between the intervention and control groups using Wald chi-square tests, and variances of the incidences were estimated using Taylor series methods. Prevalence estimates at 12 months were analyzed using Pearson chi-square statistics between the I/C groups, and logistic regression models were used to analyze the relationships further after controlling for demographic characteristics. In that study, no differences in incidence of lower respiratory illness were found. Prevalence estimates among smoking mothers (n=141) were lower in the intervention group (17.8%) than the control group (30.9%), but among infants of non-smoking mothers (n=513), there were no differences. Adjustments for tobacco smoke exposure reduced the Control minus Intervention group risk difference from 19.4% to 16.2% suggesting that much of the intervention effect on prevalence of persistent lower respiratory symptoms may have occurred through means other than reduction in tobacco smoke exposure.

In the Greenberg et al. study [5], incidence of acute lower respiratory illness during the first year of life and the prevalence of persistent lower respiratory symptoms at 1 year of age served as the respiratory health outcome. Incidence was defined based on maternal reports that her infant had a cough, wheezing, or rattling in the chest during the previous interval, and was expressed as the # of illnesses per infant-year at risk; if an infant had a health problem within the preceding interval, they were considered at risk. [5] At the 12 month follow-up, if mothers stated that their child "usually coughs" or "occasionally wheezes", the child was said to have persistent lower respiratory symptoms. We will perform similar exploratory analyses in this study looking at differences in the I/C groups.

D.9. Data Quality Control Procedures.

External quality control mechanisms will facilitate monitoring of the performance of the laboratories conducting maternal salivary cotinine, infant urine cotinine and household air nicotine assessments. This will entail repeat submission of 5% duplicate specimens from participants for analysis by each lab, and will allow an assessment of the ongoing precision of laboratory test results. Bench quality control assessment, though useful, is insufficient because laboratory performance alone is but one step in a chain of activities that could influence the test results. A program of external duplicate surveillance will allow assessment of the total system starting with the collection of a specimen in the clinics or homes, and ending with the entry of data into the RTI Data Coordinating Center computer. The duplicate biomarker data will be analyzed periodically by the Data Coordinating Center and presented to the PI and Co-PI for review. Any deficiencies detected will be investigated and corrected. These assessments of precision will be based on a 5% sample of split duplication. Collection of duplicate samples will be front-loaded to ensure the quality of data collected from each laboratory, and so that early steps can be taken to remedy any problems as necessary.

D.10. Innovations and Implications for Future Development.

The ETS study implemented by the GWUMC and their collaborating team of investigators will focus on an area of significant concern to reproductive and infant health. This ETS exposure prevention trial, conducted with pregnant women and infants during the first 12 months of life, holds promise in enriching the existing body of knowledge on the subject. Very few studies in the literature have focused on interventions specifically designed to prevent ETS exposure in infancy. Most prior studies focused on preventing ETS exposure during childhood and adulthood. With regard to the health outcomes study aim, there have been a number of limitations of previous studies which this study will hopefully address including small numbers of participants, and a primary focus on respiratory illness (either bronchial asthma or respiratory infections) as the infant health outcome of interest. This study will examine for the first time, the interaction between the risks of exposure during pregnancy versus during infancy on infant health outcomes. Furthermore, this study will focus on the efficacy of an interventional program designed for minority populations and will include very accurate monitoring of infant levels of cotinine using mass spectrometry, and correlating such levels with a variety of infant health outcomes that include, but are not restricted to, respiratory symptoms. Since the study will also monitor utilization of health care services by families recruited to the study, utilization and cost analyses may also be potentially available for analysis of the results.

E. HUMAN SUBJECTS

E.1 Population Characteristics and Recruitment & Retention. The NIH DC Initiative aims to investigate the origins of poor reproductive and child health outcomes in minority populations in the District of Columbia, and the surrounding Metropolitan area. The GWUMC intends to support this goal by implementing research protocols focused on the problem of ETS exposure during infancy. This population demonstrates a higher distribution of health risks and inadequate utilization of healthcare services, resulting in adverse health outcomes. During Phases I and II of this initiative, GWUMC successfully recruited the population of interest to various study protocols that were implemented successfully. Recruitment required a well-planned, collaborative effort to include a large number of existing healthcare facilities in the District and a culturally informed mechanism for recruitment and retention. Strong evidence for the success of these strategies exists in the recruitment and retention of minority pregnant mothers to the Project DC-HOPE randomized clinical trail in Phase II of the NIH DC Initiative. Across six participating clinical sites during Phase II, over 5,500 women were approached, 2,500 women were screened for eligibility, 1,300 were deemed eligible and 1,000 consented to participate. Only 4.5% of the participants chose to drop out of the study and 8% were lost-to-follow-up.

The ETS study, in Phase III, will be conducted in prenatal care clinics at the George Washington University Medical Center, Providence and Chartered Health Hospitals (all sites that participated in Phase II). During DCHOPE Phase II, GWUMC contributed approximately 200 women to the study who were eligible and consented to participate. Only 15 of these women dropped out or were lost-to-follow-up. The current delivery census in the GWU Hospital is approximately 2,000 deliveries annually and 27% of women delivering are DC Medicaid patients. Various strategies have been implemented at the GWU clinical site as well as at the other participating clinic sites to ensure participation and retention, including culturally informed recruitment staff, a comfortable environment for recruitment and intervention, and a patient compensation and clinic compensation program to ensure participant satisfaction and clinic staff support. Recruitment and intervention staff are well trained to be sensitive to and respectful of as participant's willingness to participate or to terminate participation in the study and are instructed to follow the requirements for informed consent as indicated by the clear Federal and Institutional guidelines.

E.2 Participation of Children. The focus of the NIH DC Initiative in Phases I and II was to reduce Infant Mortality in the District of Columbia. Participation of pregnant mothers and their infants in Phases I and II was essential to investigate the risk factors involved in infant mortality and proposed mechanisms for its reduction. During the ETS study in Phase III, the GWUMC investigators will focus on preventing risks associated with exposure to tobacco products during pregnancy and infancy. Dyads of mothers and their newly born infants will participate. Pregnant African American, Black, and Hispanic women above the age of 18 will be recruited during the prenatal period to an intervention intended to reduce the risk of environmental tobacco smoke exposure to infants in the first year of life. Every effort will be made to create a research environment that is respectful and comfortable to mothers and their infants and to fully explain any benefits or risks to infants participating in the study and the potential benefits to infants and children in the community at large. The informed consent process will be fully compliant with federal regulation to be enforced in the case of mothers consenting on behalf of their minor infants or children.

E.3 Participation of Minorities/Women. The NIH DC Initiative is a cooperative agreement that is mandated by the U.S. Congress to address issues of Infant Mortality in minority populations in the District of Columbia. During Phases I and II of this cooperative agreement, the investigators at the GWUMC successfully recruited minority women from the District and the greater Metropolitan area to their studies. Every effort was, and will continue to be, made to create a culturally informed and supportive environment and prepare materials for recruitment and for intervention that are culturally sensitive to the needs and specificities of minority populations. In addition, interventional programs delivered in the clinic environment or in the community recruit interventionists who are representative of minority groups recruited to these studies and of the communities invited to participate in these interventions. The NIH DC Initiative assembled a community advisory group during Phase I and II of the program, which played a significant role in ensuring adequate and effective participation of minority groups as designated in the Congressional mandate.

E.4 Potential Risks. In the Environmental Tobacco Smoke Exposure Reduction on Infancy Randomized Trail, we do not anticipate any untoward risk to the mother or her infant, since the intervention includes strategies to prevent recidivism of smoking behavior in the mother and strategies to eliminate or reduce the exposure of the infant to tobacco smoke. The interventions are behavioral in nature.

E.5 Minimizing Potential Risks. No risks specified. Nevertheless, while we do not anticipate risks, it may be that by answering personal questions on the survey or during conversations with the Infant Advisor, women become distressed. With respect to emotional distress, if during recruitment or one of the clinic visits (e.g., during the A-CASI screening interview or any of the in-clinic intervention sessions), a respondent becomes emotionally distressed, the study RA or IHA will provide the respondent with a list of potential referral sources. If a respondent indicates that she is in need of immediate medical or psychiatric services (e.g., she indicates that she is suicidal or possibly suicidal during the A-CASI screening interview), she will be immediately referred to a medical staff person at the clinic for further care. If, however, during a telephone interview or home visit, a participant indicates that she is suicidal or possibly suicidal, the interviewer will provide her with the toll-free Crisis Helpline telephone number from the List of Potential Referral Sources and encourage her to call to speak with a Crisis Helpline staff member. The interviewer or home visitor will be required to report the event to her supervisor immediately so that this situation can be documented as an Adverse Event Form and reported to the required IRBs.

E.6 Consent and Confidentiality. All participants including investigators, research and data management staff will be required to complete the NIH training on human subjects (http://ohsr.od.nih.gov/cbt/nonNIHpeople.html) and the institutional HIPAA training prior to patient recruitment. All patient recruitment and data management procedures will be included in the protocol for review by the Institutional Review Boards of all participating institutions prior to implementation. The environment for consenting and interviewing participants will provide the level of privacy required to maintain confidentiality and all subject-related written material will be handled and stored in compliance with federal requirements. Any suspected breach of confidentiality or proper informed consenting processes will be immediately reported to the P.I. of the study who, in turn, is responsible for reporting to the IRB and the NIH as appropriate. Finally, inclusion of minors will require informed consent by parents and all written material for consent will be at the fifth grade reading level. Participants will also be informed at the time of study enrollment that they can decline to answer any questions or discontinue the assessment, intervention or study at any time for any reason and that their decision to withdraw will not effect the medical treatment that they are receiving at the recruitment site. A copy of the consent forms will be given to participants and will identify a contact person that can be reached at the institution if they have any questions or complaints.

We will have a certificate of confidentiality to retain confidentiality of information shared by the women during the various procedures of the intervention study. Nevertheless, if a study staff member has reasonable cause to suspect child abuse or neglect, it will immediately be brought to the attention of Dr. Susan M. Blake, who will file a written report with Child Protective Services as per the laws in the District of Columbia. We have indicated to the mothers in the consent forms that we will abide by laws in the District of Columbia, and report to appropriate authorities as required by law. Similarly, women who express suicidal thoughts or ideation, or whose communications suggest they are a harm to themselves or others during the various procedures of the study will be immediately brought to the attention of their health care providers in the prenatal care clinic or primary physician in the OBGYN clinic for further referral.

E.7 Data Collection & Protection of Confidentiality. All data and biological specimens to be collected are for research purposes only. Every precaution will be taken to ensure that all data will be kept strictly confidential. We will use study ID numbers and no identifying information on the interview forms. The linkage between study ID and personal identifying information (name, address, telephone number, birth date, etc.) will be kept in a separate locked paper file cabinet accessible only to the ETS study PI, project staff, site director and Co-PI's. The linkage will be destroyed at the conclusion of the study, and any planned follow-ups. All staff on the project will receive specific training from the PI and project director on their responsibilities and office procedures to protect the confidentiality of study participants. Data storage will be handled by trained research assistants and stored in locked file cabinets in secured compartments of the GWUMC P.I.'s office. Only group data will be presented in publications and presentations.

E.9 Data and Safety Monitoring Plan. During Phases I and II, of the NIH-DC Initiative, comprehensive guidelines were developed to ensure data accuracy, confidentiality and adverse event reporting. During Phase III similar procedures will be implemented in coordination with the NIH Scientific Coordinator (Project Officer) and the Data Coordinating Center. Recruitment staff will be trained to ascertain and confirm eligibility prior to recruitment. Recruitment and intervention staff will maintain a heightened awareness for any potential risks that could be attributable to study participation and will be encouraged to report such adverse events immediately to the Project Data and Safety Monitoring Committee of the study who will in turn determine the need to report these events further to the IRB and the NICHD. Mechanisms will be instituted to deal with any adverse events that may represent a health hazard to a pregnant mother or to the infant. Reporting of such instances to the health care providers for further action will occur when needed.

The Data and Safety Monitoring Board will be responsible for periodic review of the study results and the Cumulative Averse Event Report. Based on these periodic reviews, the Data and Safety Monitoring Board will determine the safety of the study and whether the randomized intervention has reached, or is likely to reach, significance for the desired outcomes in the intervention group. The Data and Safety Monitoring Board in consultation with the Program Scientific Coordinator will determine the adequacy of the plan for safety reporting according to the study protocol and the appropriate frequency of their periodic deliberations.

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